(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 607 905 A1

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
26.06.2013 Bulletin 2013/26

(51) Int Cl.:
G01N 35/10 *(2006.01)*

(21) Application number: **11195460.8**

(22) Date of filing: **23.12.2011**

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME

(71) Applicants:
- **F. Hoffmann-La Roche AG**
  4070 Basel (CH)
  Designated Contracting States:
  AL AT BE BG CH CY CZ DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
- **Roche Diagnostics GmbH**
  68305 Mannheim (DE)
  Designated Contracting States:
  DE

(72) Inventor: **Zuppiger, Adelrich**
CH-8854 Siebnen (DE)

(74) Representative: **Gebauer, Dieter Edmund**
Splanemann
Patentanwälte Partnerschaft
Rumfordstraße 7
80469 München (DE)

(54) Method and system for discriminating bulk liquid from foam and residuals of the bulk liquid

(57) The present invention pertains to method for discriminating bulk liquid from foam and/or residuals of said bulk liquid of a sample contained in a sample vessel, comprising the following steps: providing a probe having an electric capacitance; moving said probe into said sample; repeatedly performing a pair of consecutive steps of charging and at least partially discharging said probe to generate a discharging current; measuring a quantity indicative of said discharging current for each pair of consecutive steps of charging and at least partially discharging said probe; analyzing said quantity in a manner to determine an electric resistance (R_{mess}) of said sample via said probe; discriminating said bulk liquid from said foam and/or said residuals of said bulk liquid based on a change of said electric resistance (R_{mess}) of said sample occuring when said probe contacts said bulk liquid. It further pertains to an automated system for discriminating bulk liquid from foam and/or residuals of said bulk liquid of a sample contained in a sample vessel.

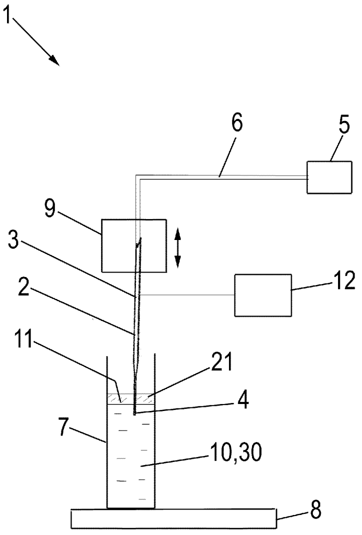

FIG. 1

EP 2 607 905 A1

Description

TECHNICAL FIELD

[0001] The present invention is in the field of analytical sample processing and relates to a method and an automated system for discriminating bulk liquid from foam which can be present on the bulk liquid of a sample contained in a sample vessel and/or from residuals of the bulk liquid which can be present on the inner side of the sample vessel and/or of a cap for closing the sample vessel.

BACKGROUND OF THE INVENTION

[0002] In automated clinical analyzers liquid samples such as bodily fluids can be tested by various clinical-chemical and immunochemical methods. In practical use, many analytical methods require precise pipetting operations in order to maintain satisfactory analytical accuracy. Usually, pump-controlled probes are being used for aspirating and discharging liquids. In order to minimize the danger of cross-contamination and facilitate probe cleaning, it is desirable to position the probe tip just below the liqid surface. The liquid can either be aspirated while keeping the probe stationary or in case of larger volumes while lowering the probe further into the vessel so as to maintain the probe tip in the liquid.

[0003] In many cases, liquid levels can greatly vary from one liquid vessel to another so that the probe tip has to be reliably positioned within the liquid before starting a pipetting operation. Hence, it is customary to detect the liquid level prior to positioning the probe. In prior art, liquid level detection is known to be based on various physical principles such as detecting light reflected from the liquid surface or measuring electric characteristics of the probe when put in contact with the liquid.

[0004] However, in some cases, especially in the case of liquids which are likely to be subject to foam formation, the reliability of results obtained by conventional liquid level detection techniques can be unacceptably low. For example, when using a technique based on the change of electric capacitance of the probe, the probe is repeatedly charged and discharged using low-frequent electric voltage signals. However, in case foam is present on the bulk liquid, the foam is likely to cause a capacitance change similar to that of the bulk liquid so that there is no clear discrimination betweeen bulk liquid and foam. Accordingly, there is a great risk that the probe will be positioned in the foam instead the bulk liquid resulting in pipetting errors. In the patent literature, liquid level detection based on capacitance change, e.g., is described in EP 89115464 A2 and US 7150190 B2.

[0005] Specifically, US 7150190 B2 adresses the problem of pipetting errors resulting from foam. It discloses a method for capacitively determining the uppermost liquid level in which the amount of time required to reach a predetermined voltage value is repeatedly measured for one sample. In order to identify foam, an averaged charging time is requested to exceed a predetermined value.

[0006] As indicated above, conventional capacitance measurements usually are based on low-frequency voltage signals typically lower than 1 kHz in order to avoid electric impedances. Otherwise, in case of applying high-frequency voltage signals which, e.g., are in the range of from 1 MHz to 1 GHz, electric impedances can be generated. Bascially, a change of the electric impedance of the probe could be used to discriminate between foam and bulk liquid. However, liquid level detection based on high-frequent impedance measurements requires sophisticated technical equipment and is rather cost-intensive. Furthermore, analyzers based on this technique can cause electric interference effects resulting in low electromagnetic compatibility so that problems with legal provisions may occur. Moreover, in case of employing plural probes, the probes will disturb each other. Liquid level detection based on high-frequency impedance measurements, e.g., is described in WO 2000019211 A1, US 5049826 A, US 5365783 and US4818492A.

[0007] Another approach to liquid level detection is given by a meaurement of the change of the Ohmic resistance of the probe occuring when the probe tip hits the bulk liquid. While foam can reliably be discriminated from bulk liquid using such technique, the liquid must be in galvanic contact with electric ground which, however, usually is not the case. Liquid level detection based on Ohmic resistance mesurements, e.g., is described in US 5843378A.

[0008] In light of the foregoing, it is an object of the invention to provide an improved method for discriminating between bulk liquid and foam which can reliably be used in case of samples tending to foam formation. These and further objects are met by a system and method according to the independent claims. Preferred embodiments of the invention are given by the dependent claims.

SUMMARY OF THE INVENTION

[0009] According to a first aspect of the invention, a new method for discriminating between bulk liquid and foam which can be present on the bulk liquid of a sample contained in a sample vessel and/or for discriminating between bulk liquid and residuals of the bulk liquid which can be present on the inner side of the sample vessel and/or a cap for closing the sample vessel is proposed.

[0010] As used herein, the term "sample" denotes any fluid of interest which, e.g., can be subject to foam formation. Specifically, samples in the sense of the term include non-biological fluids such as, but not limited to, reagents, dilutants, buffers and suspensions of magnetic particles which, e.g., can be used for nucleic acid purification purposes. Samples can also be or at least contain components of biological fluids such as, but not limited to, body fluids, e.g., blood, serum, urine, milk, saliva and cerebrospinal fluids. Specifically, samples in the sense of the term can be subject to analyses and assays in medical and pharmaceutical research and diagnosis including clinical-chemical analysis and/or immunochemical and/or biochemical analysis items. Samples can, e.g., be subject to in-vitro amplification techniques based on the polymerase chain reaction or any other reaction of the nucleic acid amplification type.

[0011] A sample contains bulk liquid free of (macroscopic) gas bubbles and may optionally contain foam present on the liquid surface of the bulk liquid and/or residuals of the bulk liquid present on the inner side of the sample vessel and, if the case may be, of a cap for closing the sample vessel. Contrary to the bulk liquid, foam contains one or more gas bubbles. In the more strict sense of the term, foam contains a plurality of small gas bubbles, the diameter of which is smaller than the dimension of the (horizontal) cross-section of the sample vessel. Alternatively or additionally, foam includes a so-called "segment region" which contains a smaller number (e.g. described by a one-digit number) of gas bubbles having a larger diameter which may even be as large as the dimension of the (horizontal) cross-section of the sample vessel. Such segment region typically occurs when the sample vessel is tilted over and then is brought in an upright position. As used herein , the term "residuals" of bulk liquid relates to portions or traces of the bulk liquid which can be present on the inner side of the sample vessel such as, but not limited to, a wetting layer and/or on the inner side of a cap for closing the sample vessel such as, but not limited to, one or more drops.

[0012] According to the invention, the method for discriminating between bulk liquid and foam and/or residuals of said bulk liquid includes a step of providing a probe, adapted to be positionable with respect to the sample so that the probe can be moved into and out of the bulk liquid. Specifically, being capacitively coupled to the ambient, the probe has an electrostatic capacitance and thus can be charged by applying an electric potential thereto. Typically, the probe is made of an electrically conductive material such as, but not limited to, a metallic material, a conductive plastic material, and an isolating material that is combined with a conductive material.

[0013] The method comprises a further step of moving the probe into the sample.

[0014] The method comprises a yet further step of repeatedly performing a pair of consecutive steps of charging the probe by applying an electric voltage (potential) thereto, and at least partially, in particular fully, discharging the probe by applying a smaller voltage (potential) thereto or by connecting the probe to electric ground so as to generate a discharging current.

[0015] The method comprises a yet further step of measuring a quantity indicative of (i.e. related to) the discharging current for each pair of consecutive steps of charging and at least partially discharging the probe simultaneously with discharging the probe. In one embodiment, the quantity indicative of the discharging current is an electric voltage signal and/or a time derivative thereof. The electric signal can, e.g., be sampled during a sampling period. In one alternative embodiment, the quantity indicative of the probe discharging current is a time interval required for fully discharging the probe so that the time required for discharging the probe is measured simultaneously with discharing the probe.

[0016] The method comprises a yet further step of analyzing the above-captioned quantity in a manner to determine an electric resistance of the sample as given by the bulk liquid and/or foam and/or residuals of the bulk liquid, via the probe.

[0017] The method comprises a yet further step of discriminating bulk liquid from foam and/or residuals of the bulk liquid based on a change of the electric resistance of the sample occuring when the probe tip contacts the bulk liquid.

[0018] As a matter of fact, the electric resistances of bulk liquid, foam and residuals of the bulk liquid normally are largely different with respect to each other so that the method of the invention enables a clear and distinct discrimination between bulk liquid and foam as well as between bulk liquid and residuals of the bulk liquid. Accordingly, the probe can reliably be positioned within the bulk liquid. As a result, liquid contained in the sample vessel can be reliably aspirated by the probe enabling an accuracy of the extracted liquid volume as high as reasonably possible.

[0019] The above-described steps for repeatedly determining the electric resistance of the sample preferably are performed simultaneously with moving the probe into the sample so as to position the probe with respect to the sample.

[0020] Specifically, in one embodiment, determining the electric resistance of the probe is periodically repeated with a repeating frequency in a range of from 1 kHz to 100 kHz. This frequency range is advantageous in that inductances can be neglected. On the other hand, analysis of the electric voltage signal obtained when discharging the probe is facilitated due to the of the voltage signal resulting in especially high accuracy.

[0021] As indicated above, in one embodiment, the quantity indicative of the discharging current is an electric voltage signal and/or a time derivative thereof. In that case, it can be preferred that the voltage signal is analyzed in a time interval starting with discharging the probe wherein the voltage signal is analyzed with respect to a voltage drop when starting discharging the probe. Accordingly, the electric resistance of the sample when the probe is galvanically coupled to bulk liquid, foam or residuals of the bulk liquid can be determined in reliable manner to discriminate bulk liquid from foam and residuals of the bulk liquid.

[0022] As indicated above, the method of the invention allows for a clear discrimination between bulk liquid and foam which can be present on the liquid surface of the bulk liquid as well as between bulk liquid and residuals of the bulk liquid which can be present on the inner wall of the sample vessel and/or the inner side of a cap for closing the sample vessel. Since a change of electric resistance of the sample can be observed when the probe contacts the bulk liquid the liquid level of the sample can also readily be determined.

[0023] In one embodiment, the method also comprises determining a change of the electric capacitance of the probe when lowering into the sample. This can be useful in some cases, especially in the case of small liquid volumes.

[0024] The invention further relates to a method for positioning a probe probe having an electric capacitance for performing pipetting operations on a sample, comprising the following steps: providing the probe; moving the probe into the sample; repeatedly performing a pair of consecutive steps of charging and at least partially discharging the probe to generate a discharging current; measuring a quantity indicative of the discharging current for each pair of consecutive steps of charging and at least partially discharging the probe and analyzing the quantity in a manner to determine an electric resistance of the sample; discriminating bulk liquid from foam and/or residuals of the bulk liquid based on a change of the electric resistance of the sample occuring when the probe tip contacts the bulk liquid; positioning the probe in the bulk liquid based on the change of the electric resistance of the sample.

[0025] In one embodiment, the probe is lowered into the bulk liquid, followed by performing a pump-controlled pipetting operation so as to suck-in or discharge liquid. The probe can be kept stationary while performing the pipetting operation and/or can moved further into the sample vessel simultaneously therewith so as to keep the probe in the bulk liquid.

[0026] According to a second aspect of the invention, a new automated system for discriminating bulk liquid from foam and/or residuals of the bulk liquid of a sample contained in a sample vessel is proposed. The system can be configured in various ways in accordance with specific demands of the user and, e.g., can be part of an automated analyzer related to various analysis items such as, but not limited to, clinical-chemical, biochemical, immunochemical analysis items.

[0027] According to the invention, the system includes at least one probe, adapted to be positionable with respect to the sample. Due to capacitive coupling to the ambient, the probe has an electric capacitance.

[0028] It further includes a positioning mechanism, adapted for positioning the probe relative to the sample, e.g., for moving the probe into and out of the bulk liquid. The probe preferrably is made of or at leasts consists an electrically conductive material.

[0029] It yet further includes a voltage source of a fixed voltage for charging the probe and an electric drain for discharging the probe.

[0030] It yet further includes a controllable switch, such as, but not limited to, a transistor, adapted to alternatively connect the probe to the voltage source for charging the probe or to the electric drain such as, but not limited to, electric ground, for at least partially (e.g. fully) discharging the probe to generate a discharging current.

[0031] The system yet further includes an electric circuitry connected to the probe, adapted to determine a quantity indicative of (related to) the discharging current. In one embodiment, the electric circuitry comprises a sample-and-hold device for sampling an electric voltage signal of the probe and/or a differentiating device for differentiating the electric voltage signal of the probe.

[0032] The system yet further includes a controller, configured to move the probe into the sample, to control the switch to repeatedly perform consecutive steps of charging and at least partially discharging the probe, and to control the electric circuitry to measure the quantity indicative of the discharging current for each pair of consecutive steps of charging and at least partially discharging the probe to determine an electric resistance of the sample, wherein the bulk liquid is discriminated from foam and/or residuals of the bulk liquid based on a change of the electric resistance of the sample occuring when the probe contacts the bulk liquid. Basicaly, the controller can be configured to peform the method steps as indicated above with respect to the method of the invention.

[0033] The system of the invention thus allows for a robust discrimination of bulk liquid and foam and/or residuals of the bulk liquid by detecting an electric resistance of the sample via the probe. It also allows for a detection of the liquid surface, that is to say, liquid level.

[0034] A major advantage of the invention is given by the fact that, in contrast to the prior art techniques, the electric resistance of the sample can reliably be used to detect the bulk liquid even in case foam is present on the liquid surface of the bulk liquid and/or residuals of the bulk liquid are present on the inner side of the sample vessel and/or cap for closing the sample vessel. Hence, bulk liquid of any sample which, e.g., can be subject to foam formation can reliably be detected.

[0035] In one embodiment of the system, the probe is configured to perform pipetting operations similar to a pipette so as to withdraw or discharge liquids when generating a negative or positive pressure therein. The probe thus has a double functionality of discriminating between bulk liquid and foam and/or between bulk liquid and residuals of the bulk liquid and pipetting liquids. Hence, pipetting operations can be combined with an exact positioning of the probe within the bulk liquid. Particularly, the probe can be lowered into the bulk liquid so as to withdraw or dispense definite liquid volumes. The probe for pipetting liquids can, e.g., be embodied as needle made of metallic material such as, but not limited to, a steel needle.

[0036] In one embodiment, the sample vessel for containing the sample comprises a vessel portion made of an electrically conductive material, wherein the conductive vessel portion is being supported by an electrically conductive support, such as but not limited to, an electrically conductive work-plate, in electric contact therewith. As a result, the capacitive coupling between the probe and the ambient, e.g., support of the sample vessel can be improved.

[0037] In one embodiment, the vessel for containing the sample is made of isolating material and is accommodated in a vessel envelope made of an electrically conductive material, wherein the conductive vessel envelope is being supported by an electrically conductive support, such as but not limited to, an electrically conductive work-plate, in electric contact therewith. As a result, the capacitive coupling between the probe and the ambient, e.g., support of the vessel can be improved.

[0038] The above-described various embodiments of the system and method of the invention can be used alone or in any combination thereof without departing from the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] Other and further objects, features and advantages of the invention will appear more fully from the following description.

[0040] The accompanying drawings, which are incorporated in and constitute a part of the specification, illustrate preferred embodiments of the invention, and together with the general description given above and the detailed description given below, serve to explain the principles of the invention.

FIG. 1	is a schematic diagram depicting a system provided with a probe for discriminating between bulk liquid and foam and/or residuals of the bulk liquid of a sample contained in a sample vessel;
FIG. 2	depicts an exemplary sample vessel containing sample;
FIG. 3	depicts an exemplary embodiment of the system of FIG. 1;
FIG. 4	depicts another exemplary embodiment of the system of FIG. 1;
FIGS. 5A-5B	are schematic diagrams for illustrating a method for discriminating between bulk liquid and foam and/or residuals of the bulk liquid using the system of FIG. 1;
FIGS. 6	is a diagram illustrating a voltage signal when charging and discharging the probe of the system of FIG. 1;
FIGS. 7A-7C	are diagrams depicting exemplary variations of resistance and capacitance of the probe of the system of FIG. 1;
FIGS. 8A-8B	depict two further exemplary embodiments of the sample vessel of the system of FIG. 1.

DETAILED DESCRIPTION OF THE INVENTION

[0041] By way of illustration, specific exemplary embodiments in which the invention may be practiced now are described. First referring to FIG. 1, by means of a schematic diagram, an exemplary embodiment of an automated system for discriminating between bulk liquid 10 and foam 21 and/or residuals 48 of the bulk liquid 10 of a liquid sample 30 contained in a sample vessel 7 is explained.

[0042] The automated system generally referred to at reference numeral 1 includes a probe 2, e.g., configured as pipette for performing pipetting operations, i.e., aspirating and dispensing liquids. Specifically, the probe 2 is provided with an inner (fluid) channel 3 which at probe tip 4 opens to the ambient. At an opposite side thereof, the probe 2 is fluidically connected to a pump 5 by a pump conduit 6 for generating a negative or positive pressure in the channel 3 so that liquids can be sucked-in or discharged according to the specific demands of the user. Since pumps for operating pipettes are well-known to those of skill in the art, e.g., from commercially available analyzers, the pump 5 is not further elucidated herein.

[0043] The probe 2 can, e.g., be configured as needle made of metallic material such as, but not limited to, stainless steel and can have a sharpened probe tip 4 for facilitating penetration of a cap (not illustrated) in case of a top-closed sample vessel 7. While only one probe 2 is shown for the purpose of illustration, those of skill in the art will recognize that more than one probe 2 can be envisaged according to the specific demands of the user.

[0044] With continued reference to FIG. 1, in the system 1, the probe 2 can be used to aspirate liquid contained in the sample vessel 7 placed on a horizontal work-plate 8. Accordingly, the sample vessel 7 is being adapted for receiving a sample 30 of interest such as a a bodily fluid, e.g., blood, urine or the like. The sample vessel 7 can, e.g., be configured as individual tube or vial or as one well of a multi-well plate.

[0045] As illustrated in FIG. 1, foam 21 can be present on the liquid surface 11 of the bulk liquid 10 of the sample 30 so that the probe tip 4 must be placed within the bulk liquid 10 in order to avoid pipetting errors caused by aspirating foam.

[0046] The probe 2 is made of an electrically conductive material such as, but not limited to, a metallic material like stainless steel. Being made of conductive material, the probe 2 has an intrinsic electrostatic capacitance C_{mess} by being capacitively coupled to the ambient, e.g., to the work-plate 8 which, e.g., can also be made of elecrically conductive material. Accordingly, the probe 2 can be charged or discharged depending on the capacitive coupling to the ambient.

[0047] With yet continued reference to FIG. 1, the system 1 further includes an automated positioning mechanism 9 for positioning the probe 2 with respect to the sample 30 contained in the sample vessel 7. Specifically, the positioning mechanism 9 can, e.g., be adapted to vertically translate the probe 2 towards and away from the sample 30 while keeping the sample vessel 7 stationary with respect to the work-plate 8 as illustrated by the double-headed arrow. Since such positioning mechanism 9 is well-known to those of skill in the art, e.g., from commercially available analyzers, it is not further elucidated herein.

[0048] Operating the positioning mechanism 9, the probe 2 can be vertically lowered to thereby reach a position where the probe tip 4 dips into the bulk liquid 10 to perform pipetting operations. Particularly, the probe tip 4 can be positioned a small distance below the liquid surface 11 in order to minimize the contact between the sample 30 and the probe 2. By placing the probe tip 4 in the bulk liquid 10 pipetting operations can reliably be performed.

[0049] In case the probe tip 4 is lowered into the sample 30, a change of the electric capacitance C_{mess} of the probe 2 can be observed. Stated more particularly, in case the probe 2 dips into the sample 3, the capacitance C_{mess} of the probe 2 is altered by the electric capacitances of the bulk liquid 10 and foam 21, respectively.

[0050] In case the probe tip 4 is lowered into the sample 30, also a change of the electric resistance R_{mess} of the sample 30 can be observed. Stated more particularly, in case the probe 2 dips into the sample 3, the electric resistance R_{mess} of the sample 30 is varied depending on the electric connection (galvanic coupling) between the probe 2 and the bulk liquid 10 and foam 21, respectively.

[0051] With continued reference to FIG. 1, in the system 1, the probe 2 is electrically connected to a discrimination device, generally referred to at reference numeral 12 which is being adapted to discriminate between the bulk liquid 10 and foam 21 and between bulk liquid 10 and residuals 48 (illustrated in FIG. 2) of the bulk liquid 10 of a sample 30 contained in the sample vessel 7.

[0052] With particular reference to FIG. 2, the sample vessel 7 can, e.g., be configured as a top-closed tube 44 provided with a cap 45 pressed into tube 44 for fixing. As indicated above, the sample 30 comprises the bulk liquid 10 wherein foam 21 can be present on the liquid surface of the bulk liquid. As can be taken from FIG. 2, in some cases, the foam 21 includes a first (lower) foam zone 46 having many small bubbles 47 (foam in the actual meaning of the word) the diameter of which is smaller than the diameter of the tube 44 and and a second (upper) foam zone 49 (denoted as "segment region" in the introductory portion) which consists of one or more very large bubbles 47 often expanding across the whole diameter of the tube 44. While the first foam zone 46 typically is a result of shaking or stirring the sample 30, the second foam region 49 is likely to be generated in case the top-closed tube 44 is tilted and then is brought in an upright position again. Furthermore, residuals 48 of the bulk liquid 10 can be present on the inner side of the tube 44 and/or the cap 45 such as a wetting layer on the inner side of the tube 44 and drops on the inner side of the cap 45. Such residuals 48 can be the result of tilting the tube 44 and then placing it in an upright position. Hence, the term "sample" as used herein includes both the bulk liquid 10 (non-foamy portion of the sample 30), the foam 21 (foamy portion of the sample 30) on the liquid surface 11 of the bulk liquid 10 and the residuals 48 of the bulk liquid 10.

[0053] With particular reference to FIG. 3, in one exemplary embodiment of the system 1, the discrimination device 12 includes a voltage source 13 of a fixed voltage (V+) electrically connected to the probe 2 by a first electric line 14_1 via a first resistor 31 having an electric resistance R_1 and a second resistor 32 having an electric resistance R_2 serially arranged with respect to each other within the first electric line 14_1. The voltage source 13 can, e.g., be configured to provide a fixed voltage (e.g. positive potential) of 24 Volts. In the embodiment shown, the first resistor 31 has a much larger electric resistance than the second resistor 32, the first resistance R_1, e.g., being as large as 1 MΩ, the second resistance R_2, e.g., being 10 kΩ.

[0054] As illustrated in FIG. 3, the discrimination device 12 further includes an electronic switch, e.g., configured as transistor 15 such as, but not limited to, a bipolar field-effect transistor (FET) . Specifically, a collector contact 16 of the transistor 15 is connected to the first electric line 14_1 in a position in-between the first and second resistors 31, 32 and an emitter contact 17 thereof is connected to electric ground 19. Furthermore, a base contact 18 of the transistor 15 is electrically connected to a microprocessor-based controller 34 by a second electric line 14_2 via a third resistor 33 having a small electric resistance R_3 of, e.g., 1 kΩ.

[0055] The controller 34 is being configured to provide the base contact 18 with an electric clock signal 35 having periodically repeated switching pulses such as, but not limited to, periodic square wave (voltage) pulses as illustrated in FIG. 2. When applying voltage pulses of the electric clock signal 35 to the base contact 18, the transistor 15 can be periodically switched on or off. Stated more particularly, in the transistor's on-state, the path between the collector contact

16 and the emitter contact 17 is electrically conductive so that an electric current can flow from the first electric line 14_1 to the emitter contact 17-connected electric ground 19 as indicated by the arrow. Otherwise, in the transistor's off-state, the electric path between the collector contact 16 and the emitter contact 17 is highly resistive so that the first electric line 14_1 is electrically separated from the electric ground 19. Accordingly, by switching the transistor 15 in on-state or off-state, the probe 2 can either be connected to the voltage source 13 or to electric ground 19.

[0056] As is further illustrated in FIG. 3, the discrimination device 12 includes an electric circuitry, generally referred to at reference numeral 20, which is being adapted to determine the electric resistance of (R_{mess}) of the sample 30 and the electric capacitance (C_{mess}) of the probe 2. In case the probe tip 4 is outside the sample 30, since neither the bulk liquid 10 nor the foam 21 or residuals 48 of the bulk liquid 10 are galvanically coupled to the probe 2, the electric resistance (R_{mess}) measured corresponds to the intrinsic electric resistance of the probe 2 which due to fact that the probe 2 is located in a gaseous atmosphere normally can be neglected. Otherwise, in case the probe tip 4 dips into the sample 30, the measured electric resistance (R_{mess}) is altered by the galvanic coupling between probe 2 and sample 30.

[0057] In one exemplary embodiment, as illustrated in FIG. 3, the electric circuitry 20 includes a sampling device 22 configured as sample-and-hold device adapted for sampling an electric voltage (potential) of the probe 2 when the probe 2 is charged or discharged depending on the transistor's on- or off-states. Correspondigly, a first sampling device input 25 is electrically connected to the probe 2 via the first electric line 14_1 by a third electric line 14_3. Specifically, a sampling device contact 24 contacts the first electric line 14_1 in a position in-between the collector contact 16 and the probe 2. Furthermore, a sampling device output 27 is electrically connected to the controller 34 via an analog-digital converter 23 configured for converting analog signals to digital signals.

[0058] A second sampling device input 26 is connected to the second electric line 14_2 by a fourth electric line 14_4 so that the sampling device 22 receives the(slightly modified) clock signal 35. Hence, the sampling device 22 can be operated synchronously with the transistor 15 except from a predetermined short time delay imposed on the voltage pulses by a delay circuitry 28 included in the fourth electric line 14_4. The delay circuitry 28 can, e.g., be configured to delay the voltage pulses by a time shift of about 10 nsec so as to account for the non-zero switching times of the transistor 15. Furthermore, the sampling periods can be selectively adapted to the switching periods.

[0059] As a result, the sampling device 22 can be operated to sample the voltage signals of the probe 2 and hold its value at a constant level for a specified time interval. For this purpose, the sample-and-hold circuitry typically includes a capacitor (not illustrated) connected to the probe 2, wherein the capacitor is being connected to a buffer amplifier (not illustrated) via a switch (not illustrated) for charging or discharging the capacitor. The analog-digital converter 23 is being used to convert the analog signals to digital signals for further processing by the controller 34.

[0060] With continued reference to FIG. 3, as above-detailed, when dipping the probe tip 4 into the sample 30 contained in the sample vessel 7, the electric resistance (R_{mess}) of the sample 30 as measured by the electric circuitry 20 changes from the intrinsic electric resistance of the probe 2 (which can be neglected) to the electric resistance of the sample 30 as given by the electric resistances of bulk liquid 10, foam 21 and residuals 48, respectively. Due to the fact that in many cases the electric resistance of the foam 10 is much higher than that of the bulk liquid 10, bulk liquid 10 and foam 21 can be reliably discriminated by determining the electric resistance (R_{mess}) of the sample 30. Furthermore, due to the fact that in many cases the electric resistance of the residuals 48 of the bulk liquid 10 is much higher than that of the bulk liquid 10, bulk liquid 10 and residuals 48 of the bulk liquid 10 can be reliably discriminated by determining the electric resistance (R_{mess}) of the sample 30.

[0061] Otherwise, when dipping the probe tip 4 into the sample 30 contained in the sample vessel 7, the electric capacitance as measured by the electric circuitry 20 changes from the intrinsic capacitance (Cmess) of the probe 2 to a capacitance modified by the capacitance of the sample 30. Depending on the specific sample, the capacitance of the bulk liquid 10 can differ from the capacitance of the foam 21 and/or residuals 48, however, can also be rather similar thereto so that the bulk liquid 10 and the foam 21 and/or residuals 48 cannot always be reliably discriminated by the change of capacitance observed when the probe tip 4 dips into the sample 30.

[0062] With particular reference to FIG. 4, in another embodiment of the system 1, the third electric line 14_3 connecting the sampling device 22 with the probe 2 and the first electric line 14_1, respectively, includes a differentiating device 29 adapted for determining a time derivative of the electric voltage of the probe 2. As is known to those of skill in the art, the differentiating device 29 usually comprises an operational amplifier 36, a fourth resistor 37 and a capacitor 38 wherein a first amplifier input 39 is connected to the probe 2 via first electric line 14_1 and capacitor 38 and a second amplifier input 40 is connected to electric ground 19. Furthermore, an amplifier output 41 is connected to the first amplifier input 39 via the fourth resistor 37. Accordingly, current flowing through the capacitor 38 is proportional to the time derivative of the voltage across the capacitor 38. Otherwise, the voltage across the fourth resistor 37 is proportional to the time derivative of the voltage across the capacitor 38. Hence, in contrast to the embodiment of FIG. 3, the time derivative of the electric voltage of the probe 2 can be sampled by the sampling device 22. The other components of the system 1 are similar to that one of FIG. 3.

[0063] With particular reference to FIGS. 5A and 5B, a process for discriminating between bulk liquid 10 and foam 21 and/or residuals 48 of the bulk liquid 10 of the sample 30 contained in the vessel 7 is explained. In this process, a pair of two consecutive steps I and II as described further below is multiply repeated when lowering the probe 2 so as to dip the probe tip 4 into the sample 30.

[0064] As illustrated in FIG. 5A, in a first step I, the transistor 15 is brought in its off-state (opened state), e.g., corresponding to the time period between two adjacent voltage pulses of the clock signal 35 applied to the base contact 18. Hence, the electric potential of the voltage source 13 is applied to the probe 2 charging the probe 2 to an extent given by the electric capacitance of the probe 2. Depending on the time period between two adjacent voltage pulses of the clock signal 35, the probe 2, e.g., is charged until saturation is reached.

[0065] As illustrated in FIG. 5B, in a second step II, the transistor 15 is brought in its on-state (closed state), e.g., corresponding to the time period of applying a voltage pulse of the clock signal 35 to the base contact 18 so that the probe 2 which has been charged in the first step I is electrically connected to ground 19 causing a discharge current to flow from the probe 2 to electric ground 19. During discharge of the probe 2, the voltage signal caused by the discharge current and/or a time derivative thereof is sampled by the sampling device 22 so that the electric resistance R_{mess} of the sample 30 can be determined. Due to the fact that the electric resistance R_{mess} of the sample 30 is greatly different in case the probe tip 4 is in the bulk liquid 10 or in the foam 21 and residuals 48, respectively, the bulk liquid 10 can be reliably discriminated from the foam 21 and residuals 48 of the bulk liquid 10. Specifially, a characteristic change of the electric resistance R_{mess} of the sample 30 can be observed when the probe tip 4 is lowered from the foam 21 into the bulk liquid 10, that is to say, when the probe tip 4 hits the liquid surface 11.

[0066] In order to position the probe tip 4 within the bulk liquid 10, the above-described pair of first and second steps I, II is periodically repeated as defined by a periodic repetition of voltage pulses of the clock signal 35 applied to both the transistor 15 and the electric circuitry 20. The clock signal 35 preferably has a frequency of 1 kHz to 100 kHz so that parasitic electric inductances can be avoided to a large extent.

[0067] The above-described process can also be used to detect the liquid surface 11 of the bulk liquid 10 by detecting the actual position of the probe tip 4 at which the probe tip 4 hits the liquid surface 11 of the bulk liquid 10, i.e., when the characteristic change of the electric resistance R_{mess} of the sample 30 occurs.

[0068] FIGS. 6 illustrates two consecutive cycles of exemplary time-dependent voltage signals as measured by the electric circuitry 20 when charging and discharging the probe 2 by periodically performing the above-described first and second steps I, II. The time is indicated by t, the voltage signal by V. Each cycle comprises the first step I of charging the probe 2 and the second step II of discharging the probe 2. It, however, is to be understood that the cycles are multiply periodically repeated based on the clock signal 35 having a frequency in the range of from 1 kHz to 100 kHz.

[0069] Specifically, in a situation in which the probe tip 4 dips into the bulk liquid 10, starting from a fully discharged probe 2 (V=0) and when charging the probe 2 in the first step (I), the voltage V of the probe 2 increases exponentially to asymptotically approach a fixed voltage level, inter alia, defined by the capacitive coupling between the probe 2 and the ambient. The increasing portion of the voltage signal denoted by "I" (corresponding to the first step I) in each cycle of the voltage signal can be described by the following formula A:

$$U = U_0 * (1 - e^{-t/R \cdot C_{mess}}) \quad (A)$$

wherein t is the time, U is the measured voltage, R is the sum of the resistances R_1, R_2 of the first and second resistors 31, 32 and the measured resistance R_{mess} of the sample 30 which is greatly different in case the probe tip 4 dips into the foam 21 and the bulk liquid 10, respectively, ($R = R_1 + R_2 + R_{mess}$), U_0 is a constant voltage value depending on the layout of the system 1, and C_{mess} is the capacitance of the probe 2. Furthermore, electric inductances are rather low and, thus, can be neglected.

[0070] Then, when discharging the charged probe 2 in the second step II, two characteristic sections of the decreasing portion, denoted as "II" (corresponding to the second step II) of the voltage signal can be oberved: a vertical first section IIa and a non-vertical second section IIb.

[0071] The first section IIa of the decreasing portion II of the voltage signal reflects the contribution of the electric resistance R_{mess} of the sample 30 and can be described by the following formula B:

$$U = U_0 / (R_2 + R_{mess}) \cdot R_{mess} \quad (B)$$

wherein U is the measured voltage, U_0 is a constant voltage value, R_2 is the resistance of the second resistor 32 and R_{mess} is the measured electric resistance of the sample 30.

[0072] The following second section IIb of the decreasing portion II of the voltage signal can be described by the following formula C:

$$U = U_{start} * (e^{-t/R \cdot C_{mess}}) \quad (C)$$

wherein t is the time, R corresponds to the sum of the electric resistance R_2 of the second resistor 32 and the measured electric resistance R_{mess} of the sample 30 and C_{mess} is the the capacitance of the probe 2. Furthermore, U_{start} is given by the formula D:

$$U_{start} = U_0 / (R_2 + R_{mess}) \cdot R_2 \quad (D)$$

wherein the symbols have the same meaning as above.

[0073] Fig. 6 also includes an enlarged view of the decreasing portion II of the voltage signal (indicated as "B"). For the reason of comparision, the enlarged view also contains the decreasing portion II (indicated as "A") which would occur when the probe tip 4 is outside the sample 30 and the decreasing portion II of a voltage signal which can be obtained when the probe tip 4 is in the foam 21 (indicated as "C").

[0074] Accordingly, as can be taken from the enlarged view of the decreasing portion II of the various voltage signals, the decreasing portion II is greatly different in case

- the probe tip 4 is outside the sample 30 (curve A)
- the the probe tip 4 is in the bulk fluid 10 (curve B)
- the the probe tip 4 is in the foam 21 (curve C)

[0075] Stated more particularly, in case the probe tip 4 is outside the sample 30 (curve A), due to the fact that the electric resistance R_{mess} of the probe 2 can be neglected (R_{mess}=0), the second portion II (decreasing flanc) of each cycle is comparably shallow without having a vertical section IIa, in other words, only having the second section IIb. Alternatively, in case the probe tip 4 is in the bulk liquid 10 (curve B), the measured electric resistance (R_{mess}) corresponds to that one of the bulk liquid 10 (R_{mess} > 0) so that the second portion II (decreasing flanc) of each cycle includes a vertical portion IIa. Yet alternatively, in case the probe tip 4 is in the foam 21 (curve C), the measured electric resistance R_{mess} of the sample 30 is higher than in the case of being in the bulk liquid 10 (R_{mess} >> 0) so that the second portion II (decreasing flanc) of each cycle includes a vertical portion IIa which is longer than in curve B.

[0076] Accordingly, by analyzing the second portion II (decreasing flanc) of each cycle of the voltage signal with respect to the measured electric resistance R_{mess} of the sample 30, in particular with respect to the length of the vertical portion IIa thereof, a change of the measured electric resistance R_{mess} of the sample 30 can be observed so that foam 21 can readily be discriminated from the bulk layer 10. Specifically, the length of the vertical portion IIa can, e.g., be compared with a pre-defined reference value to discriminate between foam 21 and bulk liquid 10. In the same manner, based on the length of the vertical portion IIa which is longer in the case the probe tip 4 is in contact with the residuals 48 of the bulk liquid 10 than in the case the probe tip 4 is in contact with the bulk liquid 10, the bulk liquid 10 can reliably be discriminated from the residuals 48 thereof.

[0077] Furthermore, by detecting the change of electric resistance R_{mess} of the sample 30, as reflected by a change of the length of the first section IIa of the decreasing portion II by repeatedly performing the above-described pair of first and second steps, it can be detected at which position of the probe 2 the probe tip 4 hits the liquid surface 11 so as to detect the liquid surface 11. Hence, by sampling the voltage signal and/or a time derivative thereof, the electric resistance R_{mess} measured via the probe 2 can also be used to detect the liquid surface 11.

[0078] The above-described process is being performed when lowering the probe 2 towards the sample 30, e.g., to position the probe tip 4 within the bulk liquid 10 for performing a pipetting operation. It, however, is also possible to detect the liquid surface 11 without performing a pipetting operation.

[0079] Reference is now made to FIGS. 7A-7C depicting exemplary variations of the electric resistance and capacitance of the probe 2 of the system of FIG. 1 when lowering the probe 2 into the sample 30 (e.g. blood serum) contained in the top-closed tube 44 illustrated in FIG. 2. In each diagram, the time (t) -dependent variation of the electric resistance R_{mess} measured via the probe 2 and electric capacitance C_{mess} of the probe 2 is illustrated. The electric resistance R_{mess} and electric capacitance C_{mess} respectively are given in arbitrary units. FIGS. 9A-9C illustrate only the downwards movement of the probe 2. Specificically, the probe 2 can be moved through an opening (not illustrated in FIG. 2) of the cap 45 or can be sharpened to penetrate the cap 45.

[0080] A typical process may start from a situation in which the probe 2 is located in a first position right above the sample vessel 7. In case the probe 2 is located in a position other than the first position, e.g., by virtue of a preceding pipetting operation, the probe 2 can be moved into the first position by means of the positioning mechanism 9. Accordingly, the process may include a step of positioning the probe 2 into the first position right above the sample vessel 7.

[0081] Next, the clock signal 35 is activated resulting in a periodically repeated execution of the first and second steps for charging and discharging the probe 2. Synchronously, the sampling device 22 is operated so as to detect the voltage signal applied to and received from the probe 2 to obtain the electric resistance R_{mess} of the sample 30. Continuously applying the clock signal 35, the probe 2 is lowered into the sample 30 until the electric resistance R_{mess} of the sample 30 indicates that the probe tip 4 in in the bulk liquid 10 and then lifted upwards to be outside the sample 30.

[0082] Specifically, FIG. 9A relates to a situation in which the sample 30 consists only of bulk liquid 10 (no foam 21 present on the liquid surface 11) and residuals 48 such as drops on lower side of the cap 45, e.g., due to sample 30 or condensed water being attached thereon. In this case, when lowering the probe 2 from the atmosphere into the sample 30, in a position denoted as "c", due to the wet cap 45 a slight change both of the electric resistance R_{mess} measured via the probe 2 and the electric capacitance C_{mess} of the probe 2 can be observed. When further lowering the probe 2 into the sample 30, a much larger change of both the electric resistance R_{mess} and the electric capacitance C_{mess} can be observed when the probe tip 4 hits the bulk liquid 10 in a position indicated by "b". A similar behaviour could be observed when the moving direction of the probe 2 is reversed which is not illustrated in FIG. 9A. Accordingly, the wet cap 45 causes a comparably small change of both the electric resistance R_{mess} and the electric capacitance C_{mess}. Otherwise, the bulk liquid 10 causes a significant change of both the electric resistance R_{mess} and the electric capacitance C_{mess}. Accordingly, the electric resistance R_{mess} measured via the probe 2 can be used to discriminate between the residuals 48 and the bulk liquid 10.

[0083] FIG. 7B relates to a situation in which the sample 30 consists of bulk liquid 10 and an overlying second foam zone 49 on the liquid surface 11. Furthermore, the lower side of the cap 45 is wetted by residuals 48, e.g., by drops attached thereon. In this case, when lowering the probe 2 from the atmosphere into the sample 30, in a position denoted as "c", due to the wet cap 45 a slight change both of the electric resistance R_{mess} and the electric capacitance C_{mess} can be observed similar to FIG. 7A. When further lowering the probe 2 into the sample 30, a much larger change of only the electric capacitance C_{mess} of the probe 2 (but not the electric resistance R_{mess}) can be observed when the probe tip 4 hits the second foam zone 49 in a position indicated by "d". When further lowering the probe 2 into the sample 30, a much larger change of both the electric resistance R_{mess} and the electric capacitance C_{mess} can be observed when the probe tip 4 hits the bulk liquid 10 in a position indicated by "b". Accordingly, the wet cap 45 causes a small change of both the electric resistance R_{mess} measured by the probe 2 and the electric capacitance C_{mess} of the probe 2, while the second foam zone 49 causes a larger change of the electric capacitance C_{mess} of the probe 2 only. Contrary thereto, the bulk liquid 10 causes a significant change of both the electric resistance R_{mess} measured by the probe 2 and the electric capacitance C_{mess} of the probe 2. Hence, there is a significant difference between the measured electric resistance R_{mess} and the electric capacitance C_{mess} of the probe 2 since the electric resistance R_{mess} measured by the probe 2 is not sensitive to the second foam zone 49.

[0084] FIG. 7C relates to a situation in which the sample 30 consists of bulk liquid 10, a first foam zone 46 and a second foam zone 49 on the liquid surface 11 and, furthermore, the lower side of the cap 45 is wetted by residuals 48 such as drops of the bulk liquid 10. In this case, when lowering the probe 2 from the air into the sample 30, in a position denoted as "c", due to the wet cap 45 a slight change both of the electric resistance R_{mess} and the electric capacitance C_{mess} can be observed similar to FIGS. 7A and 7B. When further lowering the probe 2 into the sample 30, a much larger change of only the electric capacitance C_{mess} of the probe 2 (but not the electric resistance R_{mess} of the sample 30 measured by the probe 2) can be observed when the probe tip 4 hits the second foam zone 49 in a position indicated by "d" similar to FIG. 7B. When further lowering the probe 2 into the sample 30, the electric capacitance C_{mess} of the probe 2 remains unchanged while a slight change of the electric resistance R_{mess} of the sample 30 can be observed when the probe tip 4 hits the first foam zone 46 in a position indicated by "a" and a much larger change of the electric resistance R_{mess} can be observed when the probe tip 4 hits the bulk liquid 10 in a position indicated by "b". Accordingly, the wet cap 45 causes a small change of both the electric resistance R_{mess} and the electric capacitance C_{mess}, while the second foam zone 49 causes a larger change of the electric capacitance C_{mess} of the probe 2 only. Since there is no change of the electric capacitance C_{mess} of the probe 2 when the probe tip 4 hits the first foam zone 49 and the bulk liquid 10, rspectively, the second foam zone 49 can neither be discriminated from the first foam zone 46 nor the bulk liquid 10 by means of the the electric capacitance C_{mess} of the probe 2. Otherwise, there is essentially no change of the electric resistance R_{mess} measured via the probe 2 when the probe tip 4 hits the second foam zone 49 but a significant change of the electric resistance R_{mess} measured via the probe 2 when the probe tip 4 hits the bulk liquid 10. Hence, in contrast to the electric capacitance C_{mess} of the probe 2, the electric resistance R_{mess} of the sample 30 measured via the probe 2 can be used to discriminate between the second foam zone 49 and the first foam zone 46 since the electric resistance R_{mess} is not sensitive to the second foam zone 49. Furthermore, the electric resistance R_{mess} can be used to discriminate between the second foam zone 49 and the bulk liquid 10. And, the electric resistance R_{mess} can be used to discriminate between the residuals 48 and the bulk liquid 10.

[0085] Accordingly, in case of having both a first foam zone 46 and/or a second foam zone 49 on the bulk liquid 10, the electric resistance R_{mess} measured by the probe 2 can be used to discriminate between foam 21 and bulk liquid 10. In case of also having residuals 48 of the bulk liquid 10, the electric resistance R_{mess} measured by the probe 2 can be used to discriminate between residuals 48 and bulk liquid 10. Thus, the process of the invention is considered superior to conventional methods based on capacitance detection.

[0086] Accordingly, the probe tip 4 can reliably be positioned within the bulk liquid 10 to aspirate liquid while keeping the probe 2 stationary or, in case of larger volumes, while positioning the probe tip 4 further into the bulk liquid 10 so as to maintain the probe tip 4 in a position below the liquid surface 11.

[0087] The clock signal 35 applied to both the base contact 18 of the transistor 15 and the electric circuitry 20 preferably is a medium-frequency voltage signal having a frequency in the range of from 1 kHz to 100 kHz. As a result, the voltage signal obtained from the probe 2 comprises a decreasing flank (decreasing portion II) having a steepness ideal for determining the electric resistance R_{mess} of the sample 30. In case of using a clock signal 35 comprising voltage pulses having a frequency in a range below 1 kHz, foam 21 and bulk liquid 10 can be considered as a single "conductive unit" so that foam 21 and bulk liquid 10 cannot be reliably discriminated by their conductance (very shallow flanks). Otherwise, when using a clock signal 35 comprising voltage pulses having a frequency of more than 100 kHz, there is also no clear distinction between foam 21 and bulk liquid 10 possible (very steep flanks).

[0088] In the system 1, the controller 34 is set up to control positioning of the probe 2 based on the electric resistance R_{mess} of the sample 30. The controller 34 may, e.g., be embodied as programmable logic device (microprocessor) running a computer-readable program provided with instructions to perform operations in accordance with a predetermined process routine. While not further detailed in FIG. 1, the controller 34 is electrically connected to the various system components which require control and/or provide information which include the positioning mechanism 9 for positioning the probe 2.

[0089] In the system 1, the probe 2 preferably is made of electrically conductive material such as, but not limited to, a metal like stainless steel. Furthermore, the sample vessel 7 and/or the work-plate 8 can be made of electrically isolating material such as, but not limited to, plastics.

[0090] Those of skill in the art will appreciate that the above-described process can be modified in many ways.

[0091] According to one modification, instead of charging the probe 2 in the first step I until a fixed voltage is reached, charging can also be performed for a predetermined time-interval.

[0092] According to another modification, instead of detecting the electric voltage when discharging the probe 2, the time for (fully) discharging the probe 2 can be determined.

[0093] According to yet another modification, determining the electric resistance R_{mess} of the sample 30 via the probe 2 can be combined with determining the capacitance change typcially ocurring when the probe tip 4 dips into the sample 30. This can especially be useful in case of very small sample volumes.

[0094] With particular reference to FIG. 8A, the sample vessel 7 can, e.g., consist of an electrically isolating portion 42 made of isolating material such as, but not limited to, plastics and an electrically conductive portion 43 made of electrically conductive material such as, but not limited to, an electrically conductive plastics, the latter one being used to place the sample vessel 7 on a grounded work-plate 8 made of electrically conductive material such as, but not limited to, a metal.

[0095] With particular reference to FIG. 8B, the sample vessel 7 can, e.g., consist of an electrically isolating tube 44 made of isolating material such as, but not limited to, plastics put in a conductive capsule 45 made of electrically conductive material such as, but not limited to, an electrically conductive plastics, the latter one being used to place the sample vessel 7 on a grounded work-plate 8 made of electrically conductive material such as, but not limited to, a metal.

[0096] Sample vessels 7 as illustrated in FIGS. 8A and 8B can be used to improve the capacitive coupling between the probe 2 and the work-plate 8 for measuring the electric resistance of the probe 2. Stated more particularly, by increasing the capacitive coupling therebetween, the number of charge carriers for charging the probe 2 can be increased so as to improve the signal strength of the electric signal obtained from the probe 2.

[0097] As above-detailed, in the system 1, the foamy portion of the sample 30 as well as residuals 48 of the bulk liquid 10 can be reliably discriminated from the bulk liquid 10 by a significant change of the electric resistance of the sample 30 measured via the probe 2 as a result of the difference in electric conductivity (electric resistance) between the foam 21 and residuals 48 of the bulk liquid 10 on the one hand and the bulk liquid 10 on the other hand. Furthermore, the liquid surface 11 of the bulk liquid 10 can also reliably be detected.

[0098] While exemplary embodiments have been presented in the foregoing, it is to be understood that the embodiments are only examples, and are not intended to limit the scope, applicability, or configuration in any way. Obviously many modifications and variations of the present invention are possible in light of the above description. It is therefore to be understood, that within the scope of appended claims, the invention may be practiced otherwise than as specifically devised.

Reference list

[0099]

1	System
2	Probe
3	Channel
4	Probe tip
5	Pump
6	Pump conduit
7	Sample vessel
8	Work-plate
9	Positioning mechanism
10	Bulk liquid
11	Liquid surface
12	Discrimination device
13	Voltage source
$\mathbf{14_1}$, $\mathbf{14_2}$, $\mathbf{14_3}$, $\mathbf{14_4}$	Electric line
15	Transistor
16	Collector contact
17	Emitter contact
18	Base contact
19	Ground
20	Electric circuitry
21	Foam
22	Sampling device
23	Analog-digital converter
24	Sampling device contact
25	First sampling device input

26	Second sampling device input
27	Sampling device output
28	Delay circuitry
29	Differentiating device
30	Sample
31	First resistor
32	Second resistor
33	Third resistor
34	Controller
35	Clock signal
36	Operational amplifier
37	Fourth resistor
38	Capacitor
39	First amplifier input
40	Second amplifier input
41	Amplifier output
42	Isolating portion
43	Conductive portion
44	Tube
45	Capsule
45	Cap
46	First foam zone
47	Bubble
48	Residual
49	Second foam zone

Claims

1. A method for discriminating bulk liquid (10) from foam (21) and/or residuals (48) of said bulk liquid (10) of a sample (30) contained in a sample vessel (7), comprising the following steps:

providing a probe (2) having an electric capacitance;
moving said probe into said sample(30);

repeatedly performing a pair of consecutive steps of charging and at least partially discharging said probe (2) to generate a discharging current;
measuring a quantity indicative of said discharging current for each pair of consecutive steps of charging and at least partially discharging said probe (2);
analyzing said quantity in a manner to determine an electric resistance (R_{mess}) of said sample (30) via said probe (2);
discriminating said bulk liquid (10) from said foam (21) and/or said residuals (48) of said bulk liquid (10) based on a change of said electric resistance (R_{mess}) of said sample (30) occuring when said probe (2) contacts said bulk liquid (10).

2. The method according to claim 1, wherein said pair of consecutive steps of charging and at least partially discharging said probe (2) is periodically repeated with a repeating frequency in a range of from 1 kHz to 100 kHz.

3. The method according to any one of the preceding claims 1 to 2, wherein said quantity indicative of said discharging current of said probe (2) is an electric voltage signal and/or a time derivative thereof obtained when discharging said probe (2) .

4. The method according to claim 3, wherein said electric voltage signal is sampled simultaneously with discharging said probe (2).

5. The method according to claims 3 or 4, wherein said electric voltage signal is analyzed with respect to a voltage drop at the beginning of discharging said probe (2).

6. The method according to claims 1 or 2, wherein said quantity indicative of said discharging current is a time interval required for fully discharging said probe (2).

7. The method according to any one of the preceding claims 1 to 6, wherein a liquid surface (11) of said bulk liquid (10) is determined based on said change of said electric resistance (R_{mess}) of said sample (30).

8. The method according to any one of the preceding claims 1 to 7, wherein an electric capacitance (C_{mess}) of said probe (2) is determined for each pair of consecutive steps of charging and at least partially discharging said probe (2).

9. A method for positioning a probe (2) having an electric capacitance for performing pipetting operations on a sample, comprising the following steps:

providing a probe (2) having an electric capacitance;
moving said probe (2) into a sample (30);
repeatedly performing a pair of consecutive steps of charging and at least partially discharging said probe (2) to generate a discharging current;
measuring a quantity indicative of said discharging current for each pair of consecutive steps of charging and at least partially discharging said probe (2) and analyzing said quantity in a manner to determine an electric resistance (R_{mess}) of said sample (30);
discriminating bulk liquid (10) from foam (21) and/or residuals (48) of said bulk liquid (10) based on a change of said electric resistance (R_{mess}) of said sample (30) occuring when said probe (2) contacts said bulk liquid (10);
positioning said probe (2) in said bulk liquid (10) based on said change of said electric resistance (R_{mess}) of said sample (30) .

10. The method according to claim 9, wherein said probe (2) is moved further into said bulk liquid (10) when aspirating said bulk liquid (10).

11. An automated system (1) for discriminating bulk liquid (10) from foam (21) and/or residuals (48) of said bulk liquid (10) of a sample (30) contained in a sample vessel (7), comprising:

at least one probe (2) having an electric capacitance;
a positioning mechanism (9), adapted for moving said probe (2) relative to said sample (30);
a voltage source (13) of a fixed voltage for charging said probe (2);
an electric drain (19) for discharging said probe (2) to generate a discharging current;
a controllable switch (15), adapted to alternatively connect said probe (2) to said voltage source (13) or to said

drain (19);
an electric circuitry (20) connected to said probe (2), adapted to measure a quantity indicative of said discharging current;
a controller (34), configured to move said probe (2) into said sample (30), to control said switch (15) to repeatedly perform consecutive steps of charging and at least partially discharging said probe (2), and to control said electric circuitry (20) to measure said quantity indicative of said discharging current for each pair of consecutive steps of charging and at least partially discharging said probe (2) to determine an electric resistance (R_{mess}) of said sample (30), wherein bulk liquid (10) is discriminated from foam (21) and/or residuals (48) of said bulk liquid (10) based on a change of said electric resistance (R_{mess}) of said sample (30) occuring when said probe (2) contacts said bulk liquid (10).

12. The system according to claim 11, wherein said electric circuitry (20) comprises a sample-and-hold device (22) for sampling a voltage signal and/or a time derivative thereof obtained when discharging said probe (2).

13. The system according to claims 11 or 12, wherein said probe (2) is configured to perform pipetting operations for pipetting liquids.

14. The system according to any one of the preceding claims 11 to 13, wherein said sample vessel (7) comprises a vessel portion (43) made of an electrically conductive material, said conductive vessel portion (43) being supported by an electrically conductive support (8) electrically connected therewith.

15. The system according to any one of the preceding claims 11 to 13, wherein said sample vessel (7) is made of isolating material and is accommodated in a vessel envelope (45) made of an electrically conductive material, said conductive vessel envelope (45) being supported by an electrically conductive support (8) electrically connected therewith.

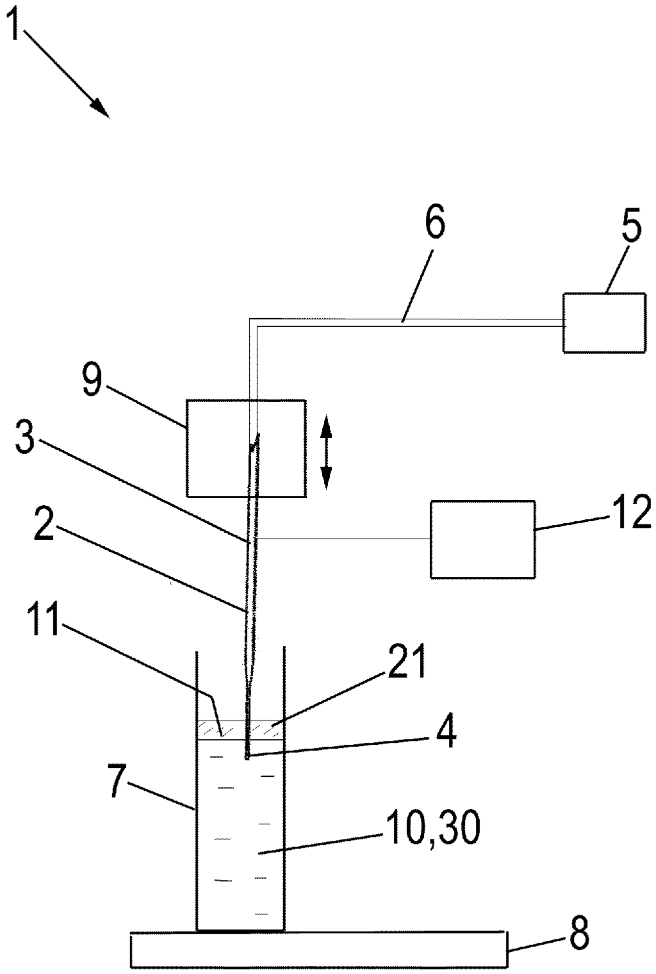

FIG. 1

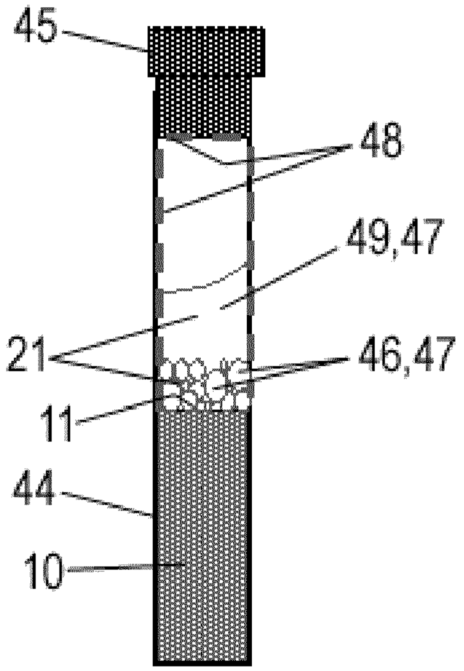

FIG. 2

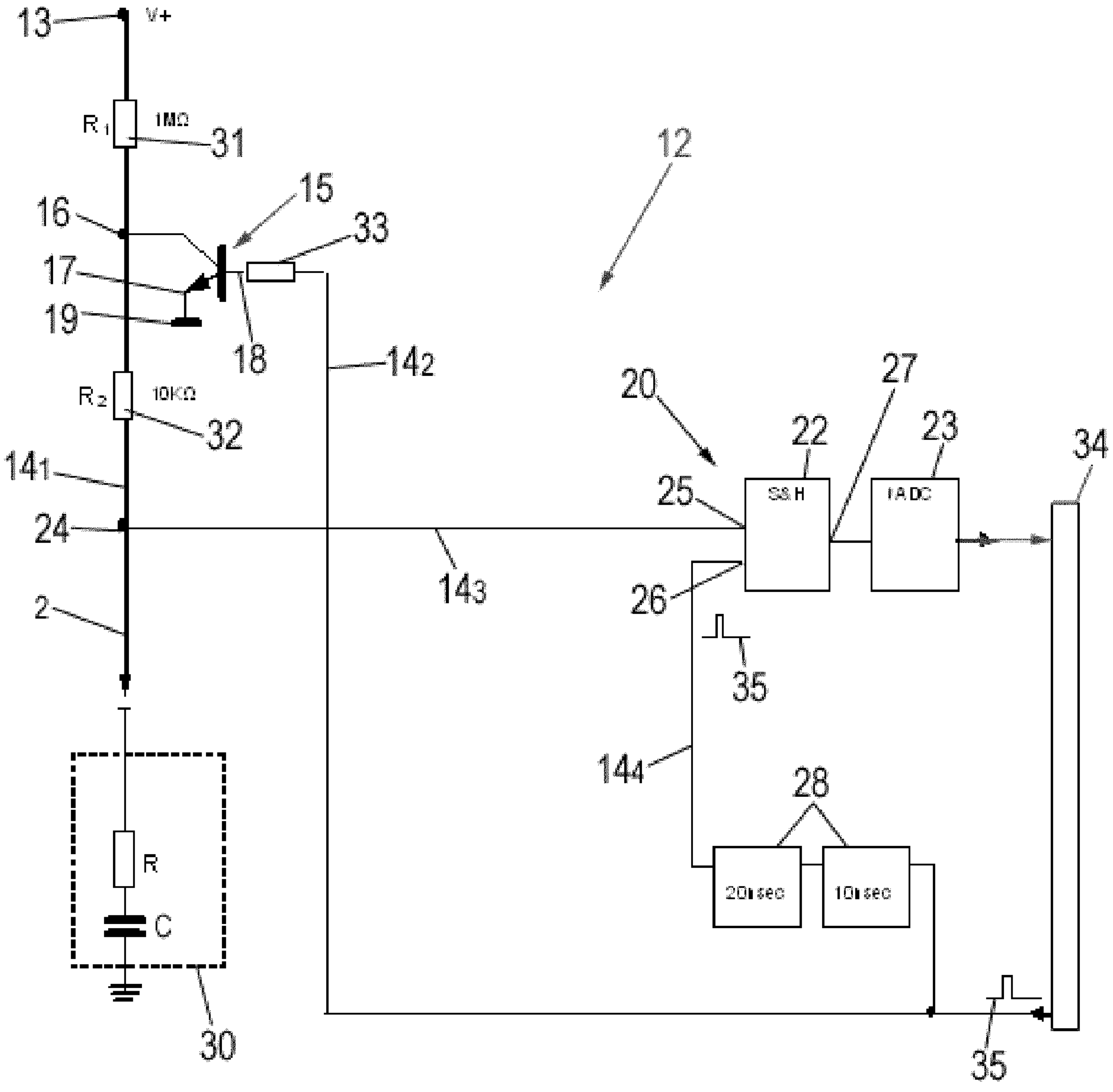
13
V+
R1
1MΩ
31
16
15
33
17
19
18
12
14₂
R2
10KΩ
32
14₁
24
14₃
2
20
25
22
S&H
27
23
ADC
34
26
35
14₄
28
20nsec
10nsec
35
R
C
30

FIG. 3

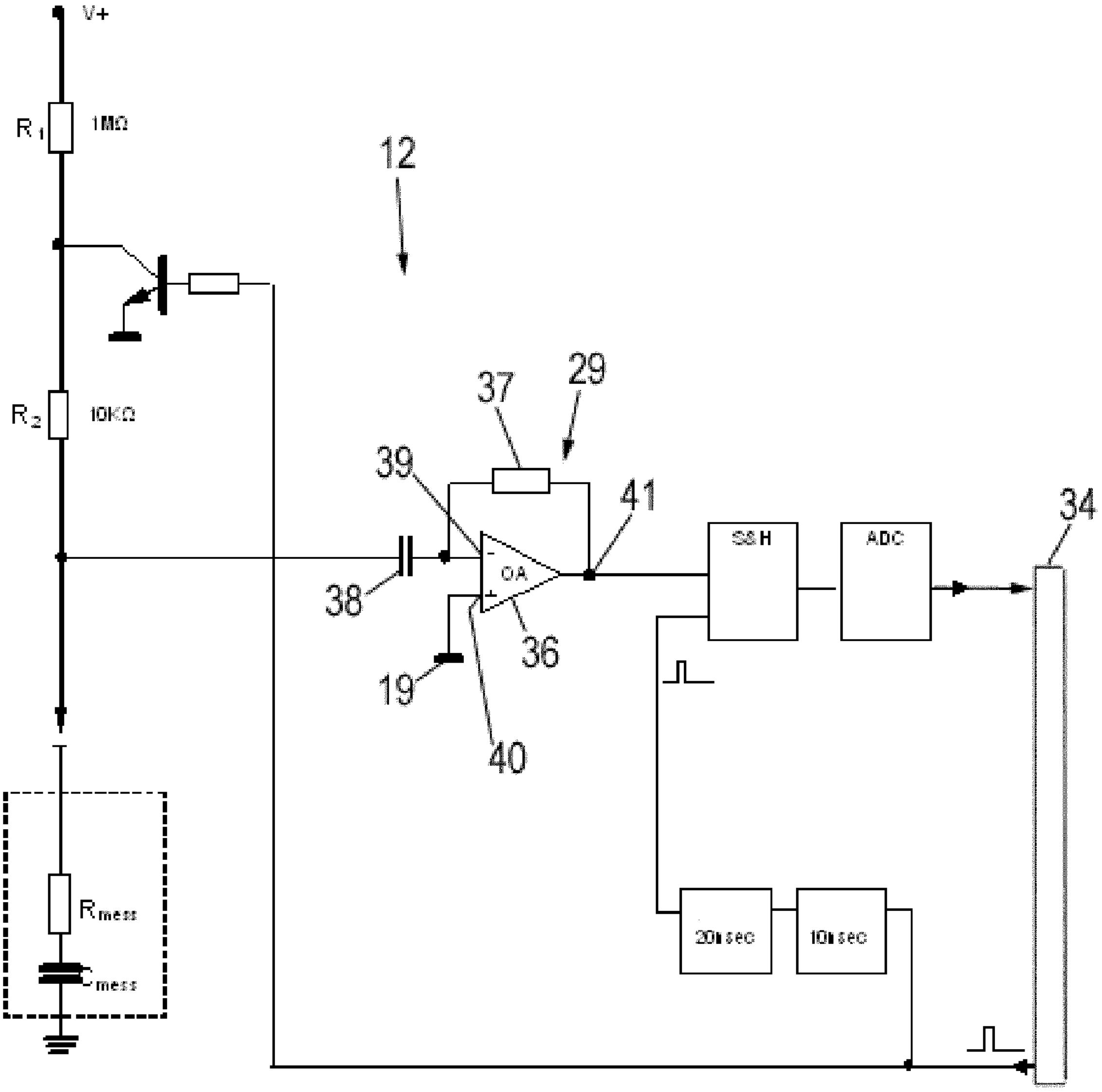
V+
R1
1MΩ
12
R2
10KΩ
37
29
39
41
34
S&H
ADC
OA
38
36
19
40
R_{mess}
C_{mess}
20µsec
10µsec

FIG. 4

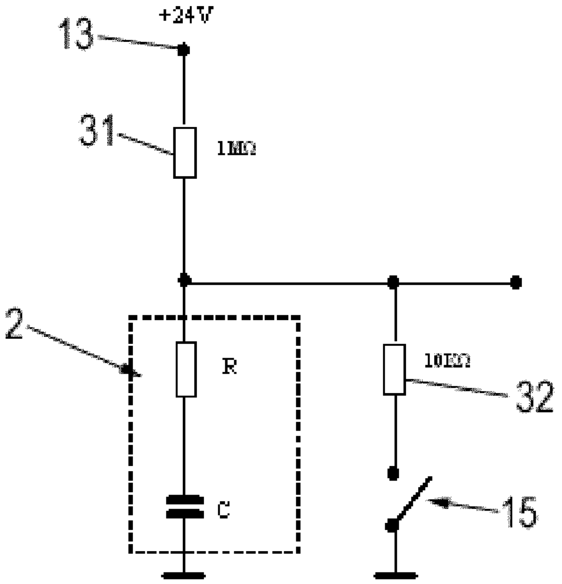

FIG. 5A

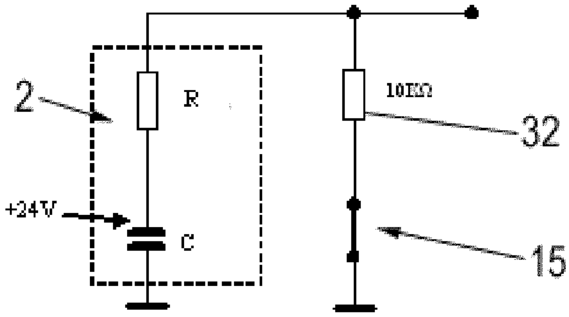

FIG. 5B

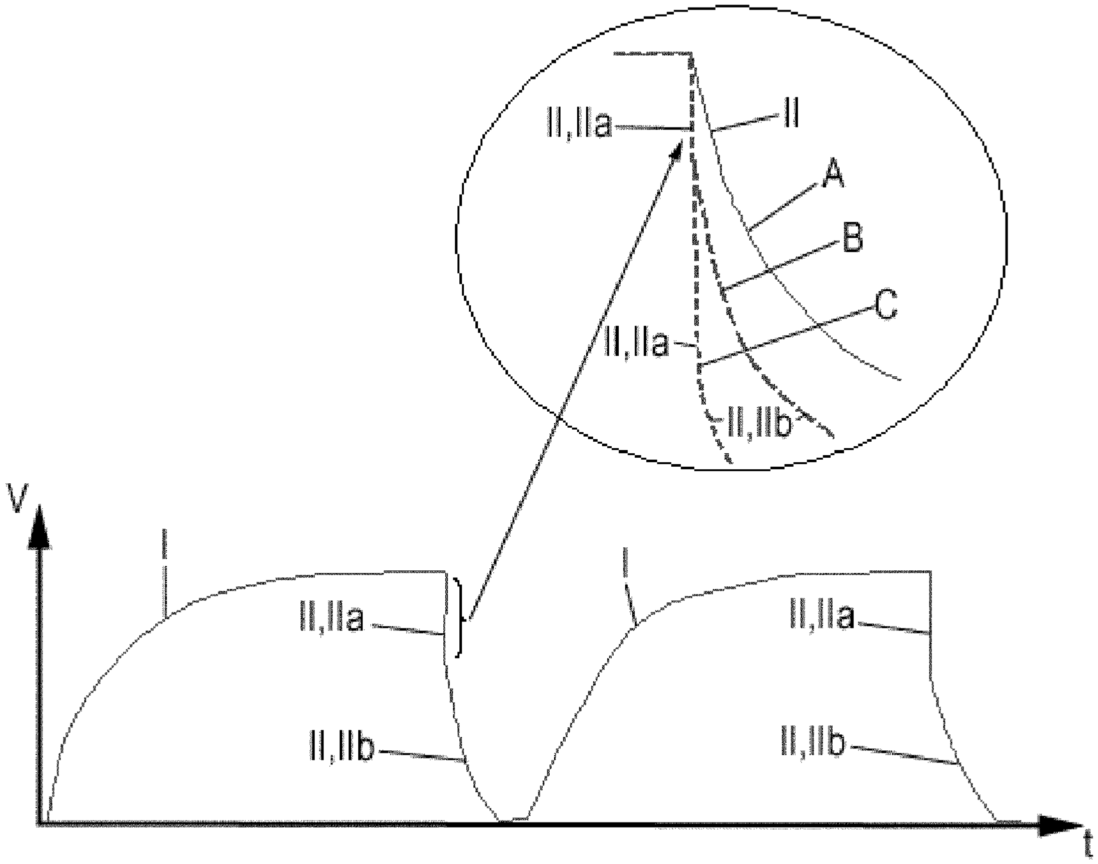

FIG. 6

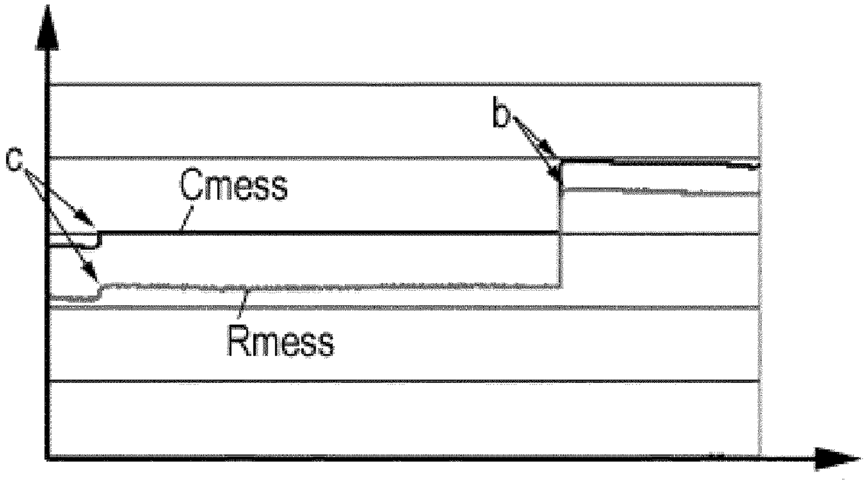

FIG. 7A

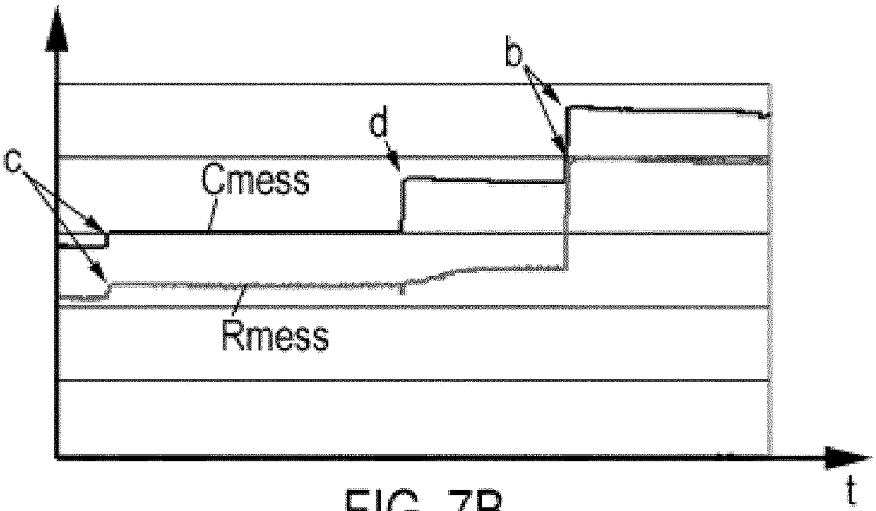

FIG. 7B

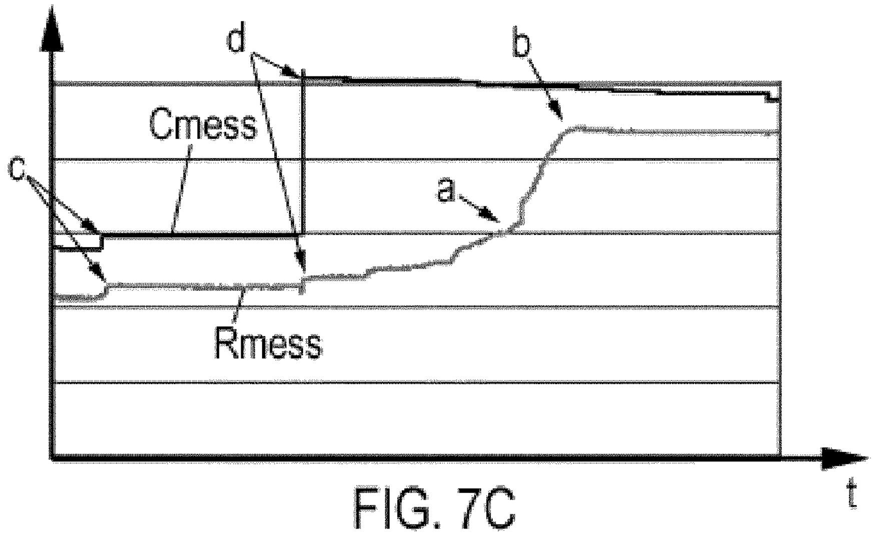

FIG. 7C

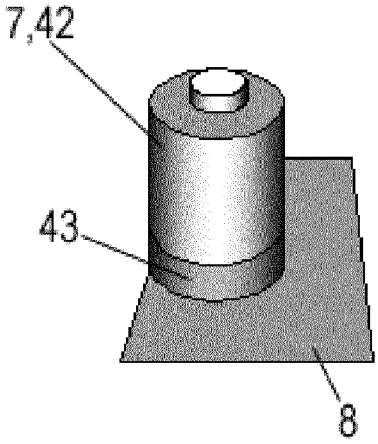

FIG. 8A

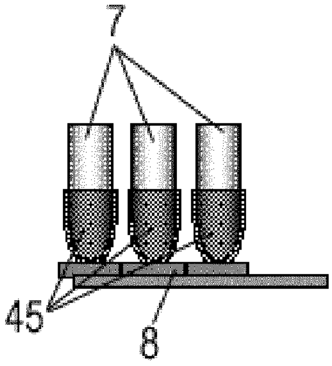

FIG. 8B

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 11 19 5460

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 6 551 558 B1 (MANN KARL-HEINZ [DE] ET AL) 22 April 2003 (2003-04-22) * abstract * * column 8, lines 55-61 * * column 11, lines 4-13, 24-29 * * column 10, lines 39-63 * * column 11, line 39 - column 12, line 20 * -----	1-15	INV. G01N35/10
X	US 6 328 934 B1 (LJUNG ARNE [SE] ET AL) 11 December 2001 (2001-12-11) * abstract * * figures 1,2a,2b * * columns 2-4 * -----	1,9,11	
			TECHNICAL FIELDS SEARCHED (IPC)
			G01N

The present search report has been drawn up for all claims

1

Place of search	Date of completion of the search	Examiner
The Hague	24 April 2012	Seifter, Achim

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons
....
& : member of the same patent family, corresponding document

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 11 19 5460

24-04-2012

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6551558 B1	22-04-2003	AT 363661 T	15-06-2007
		DE 19919305 A1	02-11-2000
		EP 1048953 A2	02-11-2000
		ES 2285980 T3	01-12-2007
		JP 4293710 B2	08-07-2009
		JP 2000338117 A	08-12-2000
		US 6551558 B1	22-04-2003
US 6328934 B1	11-12-2001	AT 377747 T	15-11-2007
		DE 69738268 T2	28-08-2008
		EP 0927339 A1	07-07-1999
		ES 2296314 T3	16-04-2008
		JP 3858084 B2	13-12-2006
		JP 2001500620 A	16-01-2001
		US 6328934 B1	11-12-2001
		WO 9812513 A1	26-03-1998

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- EP 89115464 A2 **[0004]**
- US 7150190 B2 **[0004] [0005]**
- WO 2000019211 A1 **[0006]**
- US 5049826 A **[0006]**
- US 5365783 A **[0006]**
- US 4818492 A **[0006]**
- US 5843378 A **[0007]**